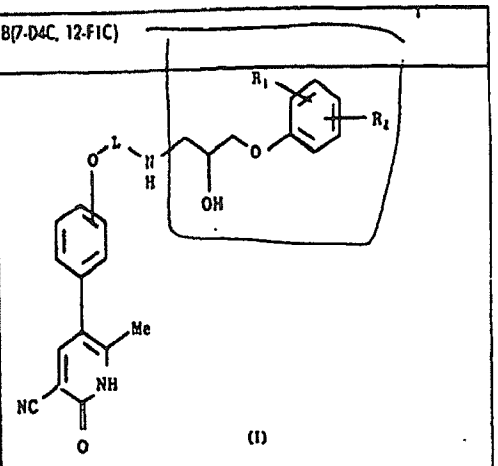
91-088869/13 803 GLAX 22.09.89
GLAXO INC *EP -419-286-A
09.08.90-US-565297 (+US-411065) (27.03.91) A61k-31/43
C07d-213/85

New phenoxy-substd. pyridone nitrile(s) - are used in treating cardiovascular disease, esp. congestive heart failure

C91-037751 R(AT BE CH DE DK ES FR GB GR IT LI LU NL SE)

B(7-D4C, 12-F1C)

Pyridone derivs. of formula (I) and their acid addn. salts are new:



(I)

R_1, R_2 = H, lower alkoxy, morpholino, CN, halo, CF_3,

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alkyl (opt. substd. by alkoxy or cycloalkylalkoxy), alkylsulphonyl, NO_2, OH, alkenyloxy, NH_2 or mono- or di-alkylamino;
L = $(CR_3R_4)_nCON(R_5)CR_6R_7CR_8R_9$ (gp.(a)) or $(CR_{10}R_{11})_p$;
R_3 - R_{11} = independently H or lower alkyl;
n = 1-3;
p = 2-6.

MORE SPECIFICALLY

L = (a; n = 1-3) or (b; p = 3) and OL is at the 4-position,
R_1-R_7, R_{10} and R_{11} = H;
R_8 and R_9 = H or Me;
either
(1) R_1 = H;
R_2 = CN, Cl or Me;
(2) R_1 = H;
R_2 = H, CN or Cl; or
(3) R_1 = H or Cl;
R_2 = H, CN or Cl at the 3-position.

USE

(I) are positive inotropic and β-adrenergic agents useful for treating congestive heart failure. Dose is 0.1-5 μg/kg 1-4 times a day.

SPECIFICALLY CLAIMED

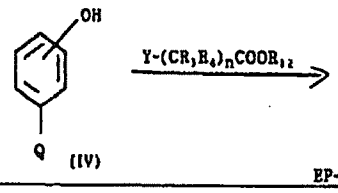
13 Cpds. (I) e.g. 5-(4-(N-(2-(3-phenoxy-2-hydroxypropylamino)ethyl)carbamoylmethoxy)phenyl)-6-methyl-2-oxo-1,2-dihydro-3- pyridinecarbonitrile (Ia);
5-(4-(N-(2-(3-(2-cyanophenoxy)-2S-hydroxypropylamino)-2-methylpropyl)carbamoylpropoxy) phenyl)-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile; and
5-(4-(N-(2-(3-(2-chlorophenoxy)-2S-hydroxypropylamino)-2-methylpropyl)carbamoylmethoxy)phenyl)-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile.

WIDER DISCLOSURE

Intermediates of formula (VI), (VII), (X), (XVII) and (XVIII) are stated to form part of the invention.

PREPARATION

(I)



(IV)

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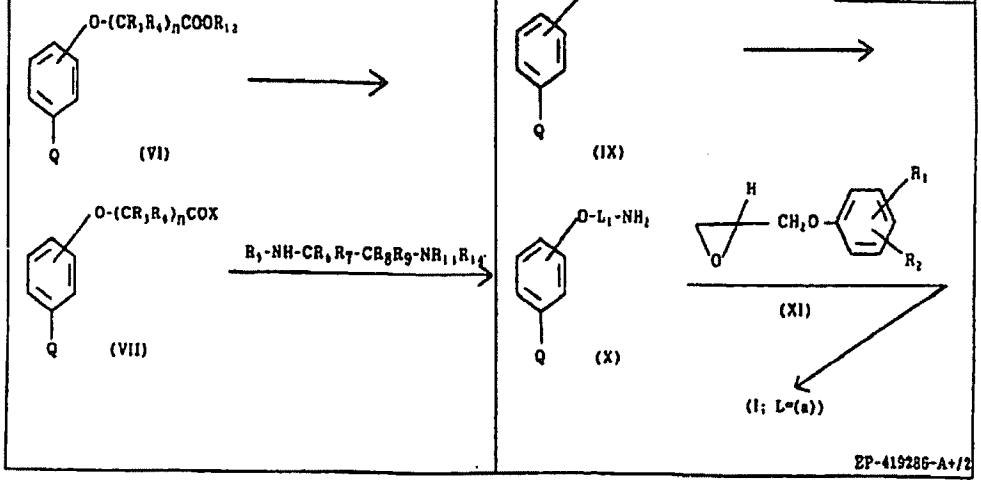

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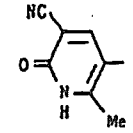
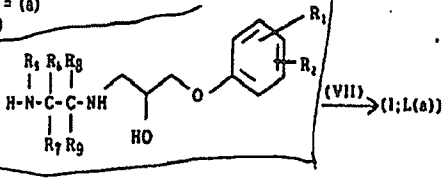
(con't)

Q =



X = leaving gp. (e.g. OH);
Y = leaving gp.;
R_{13} = H;
R_{14} = amino protecting gp.;
or R_{13} + R_{14} = amino protecting gp.;
L_1 = (a)

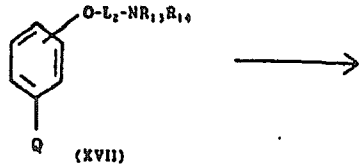
(II)



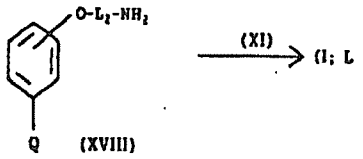
(VII) → (I; L(a))

(III)

(IV) $Y-(CR_{10}R_{11})_pNR_{13}R_{14}$ →



(XVII)



(XVIII)

(XI) → (I; L = (b))

L_2 = (b)

EXAMPLE

A soln. of 500 mg 5-(4-carboxymethoxyphenyl -6-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile, 407 mg (±)-

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-N-(2-aminoethyl)-2-hydroxy-3-phenoxypropylamine and 316 mg diethyl cyanophosphonate in 10 ml DMF is cooled (ice bath) and treated dropwise with 540 µl Et_3N in 2 ml DMF. The mixt. is allowed to slowly warm to room temp., stirred overnight under N_2 then evapd. in vacuo. The residue is chromatographed over silica gel, eluting with $CHCl_3$/MeOH/NH_4OH (90:10:2). The solid is recryst. from EtOAc/MeOH to give 185 mg (21%) (Ia), m.pt. 136-138°C. (29pp985HBDwgNo0/0)

(E) ISR: No Search Report.